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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Meir STERN et al.

Confirmation no.: 1887

Application No.: 10/699,582

Group Art Unit: 3763

Filed: October 31, 2003

Examiner:

For: TRANSDERMAL DELIVERY SYSTEM FOR DRIED PARTICULATE OR LYOPHILIZED MEDICATIONS

Attorney Docket No.: 85189-5300

SUBMISSION OF CERTIFIED PRIORITY DOCUMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Applicants have claimed priority under 35 U.S.C. § 119 of Application No. IL152574.5 filed October 31, 2002 in Israel. In support of this claim, a certified copy of said application is submitted herewith.

No fee or certification is believed to be due for this submission. Should any fees be required, however, please charge such fees to Winston & Strawn LLP Deposit Account No. 50-1814.

Respectfully submitted,

Date: 3-22-04

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חוק הפטנטים, תשכ"ז - 1967
PATENT LAW, 5727 - 1967

בקשה לפטנט
Application for Patent

לשימוש הלשכה
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מספר: Number	152574
תאריך: Date	31-10-2002
הוקדם/נדחה Ante/Post-dated	

אני, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)
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Owner, by virtue of The Law and Assignment — בעל אמצאה מכח הדין והעברה

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(בעברית) (Hebrew): מערכת להולכה דרך העור של פריטים יבשים או תרופות מיובשות

(באנגלית) (English): TRANSDERMAL DELIVERY SYSTEM FOR DRIED PARTICULATE OR LYOPHILIZED MEDICATIONS

hereby apply for a patent to be granted to me in respect thereof. — מבקש בזאת כי ינתן לי עליה פטנט

*בקשת חלוקה - Application of Division	*בקשת פטנט מוסף - Application for Patent Addition	*דרישה דין קדימה Priority Claim		
מבקשת פטנט from Application	*לבקשה/לפטנט to Patent/Appl.	מספר/סימן Number/Mark	תאריך Date	מדינת האגוד Convention Country
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TRANSDERMAL DELIVERY SYSTEM FOR DRIED PARTICULATE OR LYOPHILIZED MEDICATIONS

מערכת להולכה דרך העור של תרופות בצורת אבקות יבשות או ליופיליזטים

TRANSPHARMA002 IL

TRANSDERMAL DELIVERY SYSTEM FOR DRIED PARTICULATE OR LYOPHILIZED MEDICATIONS

FIELD OF THE INVENTION

The present invention relates generally to the field of drug formulations for use in conjunction with a transdermal delivery system and relates specifically to a drug-containing matrix that is useful as a component in a transdermal device for effective transdermal delivery of dried or lyophilized medications, in conjunction with an apparatus that operates by forming channels in the skin of a subject.

BACKGROUND OF THE INVENTION

There are clearly many theoretical advantages to the transdermal delivery of dried or lyophilized drugs instead of commercially available oral or injectable forms of these drugs. Delivery of a drug across the skin of a patient obviates the problems of drug inactivation by gastrointestinal fluids or enzymes, fluctuations in absorption from the gastrointestinal tract, and hepatic first pass inactivation, while also avoiding the inconvenience of injection. However, hitherto proposed devices or methods for transdermal delivery of dried particulate or lyophilized drug substances have not successfully yielded reliable uptake and sustained serum levels of the active substance.

Generally speaking the objective of transdermal drug delivery has been tackled using one of two complementary approaches known in the art. One approach provides formulations of drugs that may be applied to the skin in the form of patches, or films or matrices of varying compositions, and the alternative approach utilizes a method of puncturing the skin or otherwise disrupting the impermeable layers of the skin to facilitate the entry of drugs into the systemic circulation.

Transdermal patches

Patches or matrices almost invariably comprise some type of penetration enhancer and some type of adhesive layer, and are known to cause irritation or edema and to produce non-uniform rates and levels of drug uptake among different patients and different skin types.

There are two prevalent types of transdermal patch design, namely the reservoir type where the drug is contained within a reservoir having a basal surface that is

permeable to the drug, and a matrix type, where the drug is dispersed in a polymer layer affixed to the skin. Both types of device also typically include a backing layer and an inner release liner layer that is removed prior to use.

EP 0391172 describes a transdermal patch having a matrix composed of a water-insoluble material that contains islands of solid particles of drug in a water-soluble/swellable polymer and an underlayer that controls the amount of water vapor passing from the skin to the matrix. The matrix is said to be activated by water vapor from the skin.

Compositions or devices in the form of specific types of patches adapted for the transdermal delivery of dry powder or lyophilized drugs have been disclosed for example in EPB 912239 to PowderJect Research Ltd. that discloses "Method for providing dense particle compositions for use in transdermal particle delivery".

Methods for transdermal delivery of powders are also disclosed in US 5983135 to Avrahami.

Methods for transdermal delivery of Growth Hormone Releasing Peptide (GHRP) are disclosed in WO 98/08492 to Novo Nordisk. Methods for transdermal delivery of growth hormone releasing peptide are also disclosed in conjunction with iontophoresis in scientific publications by Singh et al. (J. Controlled Release, 33, 293-298, 1995); Lau, et al. (Pharmaceutical Research 11, 1742-1746, 1994); Kumar et al. (J. Controlled Release 18, 213-220, 1992); Ellens et al. (Int. J. Pharm. 159, 1-11, 1997). In those publications, the onset of the electrical current induces the influx of GHRP across the skin, and cessation of the current terminates the influx of the peptide.

Transdermal delivery apparatus

Electrotransport or ionotophoretic drug delivery devices have also been disclosed as being useful for the delivery of dried or lyophilized drugs for which it is anticipated that transdermal delivery would be advantageous. US Patents 6,169,920 and 6,317,629 to Alza for example disclose iontophoretic drug delivery apparatus, while US Patent 5,983,130 to Alza discloses and electrotransport agent delivery method and apparatus suitable for ionizable drugs.

Electroporation is also well known in the art as a method to increase pore size by application of an electric field. Electroporation is disclosed as a means for transiently decreasing the electrical resistance of the stratum corneum and increasing the

transdermal flux of small molecules by applying an electric field to increase the size of existing pores (Chizmadzhev et al., Biophysics Journal, 1998, 74(2), 843-856).

U.S. Patent 5,019,034 to Weaver et al. describes apparatus for applying high voltage, short duration electrical pulses on the skin to produce electroporation.

WO 97/07734 to Eppstein et al. discloses thermal ablation of the stratum corneum using an electrically resistive element in contact with the stratum corneum, such that a high current through the element causes a general heating of tissue in its vicinity, most particularly the stratum corneum the 10-50 micron thick outermost layer of the skin.

U.S. Patents 5,885,211, 6,022,316, 6,142,939 and 6,173,202 to Eppstein et al., which are incorporated herein by reference, describe methods for forming micro-pores in the stratum corneum by heating tissue-bound water above the vapor point with a heat-conducting element, so as to enhance transdermal transport of an analyte or active substance. Further enhancement techniques include the use of sonic energy, pressure, and chemical enhancers.

U.S. Patents 3,964,482 to Gerstel, 6,050,988 to Zuck, and 6,083,196 to Trautman et al. describe other apparatus and methods for facilitating transdermal delivery of a substance.

U.S. Patent 6,148,232 to Avrahami, which is incorporated herein in its entirety by reference, describes apparatus for applying electrodes at respective points on skin of a subject and applying electrical energy between two or more of the electrodes to cause resistive heating and subsequent ablation of the stratum corneum primarily in an area intermediate the respective points. Various techniques for limiting ablation to the stratum corneum are described, including spacing of the electrodes and monitoring the electrical resistance of skin between adjacent electrodes.

The Device for Transdermal Drug Delivery and Analyte Extraction of the type disclosed in US 6,148,232, and various improvements to that invention including those disclosed in PCT/IL02/00376, and PCT/IL02/00319, are also referred to hereinafter in the specification by the term "ViaDerm".

There is thus an unmet need for reliable and safe compositions and methods for transdermal delivery of drug in dried particulate or lyophilized form. The advantages of this approach would be particularly striking for peptides and polypeptides, as well as other bioactive drug substances including but not limited to oligo- or poly- nucleotides.

SUMMARY OF THE INVENTION

It is an object of some aspects of the present invention to provide an effective system and methods for transdermal delivery of an active dried or lyophilized substance.

It is another object of some aspects of the present invention to provide an apparatus and methods for ablating the skin and transdermally delivering an active dried or lyophilized substance to the pretreated skin.

It is an additional object of some aspects of the present invention to provide apparatus and methods for transdermally delivering an active dried or lyophilized substance using a suitable medical skin patch.

It is still another object of some aspects of the present invention to provide apparatus and methods for ablating the skin and transdermally delivering an active dried or lyophilized hydrophilic substance using a medical skin patch.

It is still a further object of some aspects of the present invention to provide a medical skin patch consisting essentially of a hydrophilic active dried formulation.

It is still another object of some aspects of the present invention to provide printed patches and method of preparation thereof, for transdermal delivery of an active dried substance.

The compositions and the methods of the present invention are suitable for use with many of the patches known in the art, though application of the drug with the system of the present invention using a printed patch has proven particularly effective and has yielded unexpectedly advantageous exemplary results.

It is now disclosed for the first time that use of a patch comprising a dried or lyophilized pharmaceutical composition comprising a therapeutically active substance, placed on an area of the skin pretreated by an apparatus that generates micro-channels provides unexpectedly therapeutically effective serum levels of the drug.

These results were totally unexpected, due to the fact that usually in transdermal delivery bioavailability rates are low (3-20%). Moreover, the unexpected results were achieved using even a very large molecule, with low diffusion coefficient.

The principles of the invention are exemplified hereinbelow using human growth hormone, having a molecular weight of 22 kDa. It is explicitly intended that the compositions and methods comprising the system of the invention are applicable to a wide variety of polypeptides, peptides, polynucleotides, oligonucleotides, and other

bioactive molecules, including but not limited to steroid hormones and various types of growth factors and hormones.

According to a first aspect, the system of the present invention comprises an apparatus that creates channels in the stratum corneum, and is then removed from the skin, as a means for enhancing the transdermal delivery of a substance from a patch subsequently placed on the skin.

According to a currently preferred embodiment, the system of the invention comprises an apparatus that creates micro-channels, as defined herein, as a means for enhancing the transdermal delivery of a substance from a skin patch subsequently placed on the skin. The term "micro-channel" as used in the context of the present patent application refers to a pathway generally extending from the surface of the skin through all or a significant part of the stratum corneum, through which pathway molecules can diffuse.

According to a second aspect, the system of the present invention comprises a medical patch comprising a dried or lyophilized active drug substance wherein the patch is placed over the treated region in which the micro-channels were generated. The patch may comprise any suitable composition and be of any suitable geometry provided that it is adapted for stable and, optionally microbiologically controlled, aseptic or sterile, storage of the drug species prior to its use.

According to one embodiment, the system of the present invention comprises a patch comprising a dried or lyophilized pharmaceutical composition comprising at least one therapeutically active substance. The therapeutically active substance may be hydrophilic or the patch may comprise an additional hydrophilic dried substance. In a currently preferred embodiment, the additional hydrophilic substance is mannitol. The patch may further comprise at least one of the following: a backing layer, an adhesive, a preservative, anti-oxidants, a buffering agent and other additives as are well known in the art.

According to a currently preferred embodiment, the present invention provides a printed patch consisting essentially a dried or lyophilized pharmaceutical composition comprising at least one therapeutically active substance. The therapeutically active substance may be hydrophilic or the dried pharmaceutical composition may comprise an additional hydrophilic dried substance. In a currently preferred embodiment, the additional hydrophilic substance is mannitol. The printed patch may further comprise at

least one of the following: a backing layer, an adhesive, a preservative, anti-oxidants, a buffering agent and other additives as are well known in the art.

In another currently preferred embodiment, the present invention provides methods for preparing a printed patch containing a therapeutically active agent comprising:

a. preparing a pharmaceutical solution or suspension comprising at least one therapeutically active agent; and

b. placing at least one droplet of an accurate volume of the solution of (a) on a suitable matrix; and

c. drying the matrix of (b) wherein upon drying the therapeutic activity of the therapeutically active agent of (a) is retained.

The simplicity of the essential ingredients of the patch stems from the fact that the patch is specifically designed for use in conjunction with the apparatus for generating micro-channels in the skin of the subject.

According to additional currently preferred embodiments, the present invention provides methods of transdermal administration of a dried or lyophilized pharmaceutical composition comprising at least one therapeutically active substance using a patch according to embodiments of the present invention. In one embodiment the method comprises: generating at least one micro-channel in a region of the skin of a subject, and affixing a patch comprising the dried or lyophilized pharmaceutical composition to the region of skin in which the micro-channels are present. The method of the invention provides a serum concentration of at least 50 ng/ml of the therapeutically active substance.

According to preferred embodiments the therapeutically active substance in the context of the dried or lyophilized pharmaceutical composition of the invention is selected from the group consisting of polypeptides, peptides, polynucleotides, oligonucleotides, and pharmaceutically acceptable salts thereof. A currently more preferred exemplary embodiment is human Growth Hormone (hGH).

According to certain preferred embodiments, the present invention incorporates the techniques for creating micro-channels by inducing ablation of the stratum corneum, using radio frequency (RF) energy, including the apparatus referred to as ViaDerm or MicroDerm, disclosed in one or more of the following: U.S. Patent No. 6,148,232 to Avrahami; US Patent No. 5,983,135 to Avrahami; PCT Patent Application No. WO 01/85234; US Patent Application No. US2002/0038101; US Patent Application

US2002/0058936; and PCT Patent Applications No. PCT/IL02/00319 and PCT/IL02/00376; the content of which being incorporated herein in their entirety. It is however emphasized that although some preferred embodiments of the present invention relate to transdermal delivery obtained by ablating the skin by the aforementioned apparatus, substantially any method known in the art for generating channels in the skin of a subject may be used.

In one currently preferred embodiment of the invention, the system comprises an apparatus for facilitating transdermal delivery of a drug through the skin of a subject, said apparatus comprising:

a. an electrode cartridge, optionally removable, comprising at least one electrode, preferably a plurality of electrodes; and

b. a main unit comprising a control unit which is adapted to apply electrical energy to the electrode when the electrode is in vicinity of the skin, typically generating current flow or one or more sparks, enabling ablation of stratum corneum in an area beneath the electrode, thereby generating at least one micro-channel.

In another embodiment, the control unit of the apparatus comprises circuitry to control the magnitude, frequency, and/or duration of the electrical energy delivered to an electrode, so as to control the current flow or spark generation, and thus the width, depth and shape of the formed micro-channel. Preferably, the electrical energy is at radio frequency.

In a currently preferred embodiment, the electrode cartridge of the apparatus comprises a plurality of electrodes enabling to generate a plurality of micro-channels, wherein the micro-channels are of uniform shape and dimensions.

The present invention will be more fully understood from the following detailed description of the preferred embodiments thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a view of a printed patch consisting of rhGH dried solution and a polyester screen.

Figure 2 is an images of a commercial diluted rhGH dried solution air-dried over a polyester screen.

Figure 3 is an images of mannitol mixed with methylene blue solution air-dried over a polyester screen.

Figure 4 is an image of sucrose solution air-dried over a polyester screen.

Figure 5 are images of a polyester screen before (left panel) and after (right panel) screen were immersed in sucrose solution and air-dried.

Figure 6 exhibits the levels of rhGH in the serum of rats.

Figure 7 shows IGF-I levels in the serum of rats.

Figure 8 is a view of a printed patch.

Figure 9 exhibits HPLC analysis of the printed patches.

Figure 10 shows the serum levels of rhGH, applied through transdermal printed patches and through subcutaneous injections.

Figure 11 presents AUC values normalized to administration of 0.1mg rhGH.

Figures 12 exhibits top (a), side (b) and bottom (c) views of the control unit of a ViaDerm device.

Figure 13 is a photograph of the microelectrodes array utilized to create micro-channels in the skin.

Figure 14 is a hematoxylin and eosin stained histological section of porcine ear skin treated by ViaDerm.

Figure 15 presents the transepidermal water loss (TEWL) from porcine ear skins, after generation of micro-channels or after removal of the stratum corneum.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides formulations, methods and pharmaceutical technologies for delivering dried and lyophilized medications, preferably of hygroscopic formulations, through treated skin in which micro-channels have been generated. The current transdermal patches are designed to deliver drug molecules through the stratum corneum (SC). As such they have several characteristics:

a. The delivery of the molecules occurs through all the area under the patch.
b. The interface between the patch and the skin tends to be hydrophobic. This facilitates delivery of drug molecules from one hydrophobic matrix (patch) to the other (SC).
c. The patches usually contain enhancers. The purpose of these molecules is to change and disrupt the structure of the SC, thus elevating the solubility of the drug molecules in the SC matrix. Enhancers are also responsible for undesired side effects like erythema, edema or pruritis.

Micro-channel or electroporation treatment creates aqueous microchannels through the SC into the epidermis, thus drug molecules do not need to pass through the lipoid SC in order to get into viable tissues. This has several implications:

1. The delivery of the molecules occurs mainly through the microchannels, which occupy less than 1% of the treated skin area.
2. The transdermal delivery rate of substances through the microchannels is not restricted by the limited permeability of the SC.
3. There is no need to include enhancers in the formulations, thus improving skin safety.

Based on these considerations, the system of the present invention is highly suitable for delivery of dried or lyophilized hydrophilic macromolecules through the new skin environment, which is created by the ablation of the stratum corneum. The main advantage of using dried or lyophilized formulations is the potential stability of the pharmaceutically active ingredients as compared with liquid formulations. This advantage is especially relevant for active ingredients in the form of peptides and proteins. Accordingly, a variety of formulations may provide efficient delivery of a variety of drugs, particularly and advantageously of dried or lyophilized hygroscopic formulations. As a consequence, the system of the present invention does not necessitate the use of permeation enhancers for transdermal drug delivery and is therefore not susceptible to the problems attendant therewith, particularly irritation. Irritation occurs as the skin reacts to topically applied substances, particularly those maintained under occlusion, by blistering or reddening accompanied by unpleasant burning, itching, and stinging sensations. It is desirable to avoid or to keep the number of possibly irritating substances in a transdermal delivery system to a minimum.

The term "micro-channel" as used in the context of the present specification and claims refers to a pathway generally extending from the surface of the skin through all or a significant part of the stratum corneum and may reach into the epidermis or dermis, through which molecules can diffuse. Although some preferred embodiments of the present invention are described with respect to ablating the stratum corneum by electric current or spark generation, preferably at radio frequency (RF), substantially any method known in the art for generating channels in the skin of a subject may be used (see e.g. U.S. Patents 5,885,211, 6,022,316, 6,142,939 6,173,202, 6,148,232 and International Patent Applications PCT/IL02/00376 and PCT/IL02/00319). The term "micro-pore" is used interchangeably herein.

The term "new skin environment" as used herein, denotes a skin region created by the ablation of the stratum corneum and formation of at least one micro-channel, using the system of the present invention.

Suitable drugs for use in conjunction with the principles of the invention are dried or lyophilized large molecules, including a wide variety of polypeptides, peptides, polynucleotides, oligonucleotides, and other bioactive molecules, including but not limited to steroid hormones, insulin, proinsulin, follicle stimulating hormone, insulin like growth factor-1 and insulin like growth factor-2, platelet derived growth factor, epidermal growth factor, fibroblast growth factors, nerve growth factor, colony stimulating factors, transforming growth factors, tumor necrosis factor, calcitonin, parathyroid hormone, growth hormone, bone morphogenic protein, erythropoietin, hemopoietic growth factors and luteinizing hormone, calcitonin; glucagon; clotting factors such as factor VIIIC, factor IX, tissue factor, and von Willebrand factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or tissue-type plasminogen activator, including human tissue-type plasminogen activator (t-PA); bombesin; thrombin; enkephalinase; a collagen; a collagen domain; mullerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; Dnase; inhibin; activin; vascular endothelial growth factor; receptors for hormones or growth factors; integrin; protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3, -4, -5, or -6 (NT-3, NT-4, NT-5, or NT-6, CD proteins such as CD-3, CD-4, CD-8, and CD-19; osteoinductive factors; immunotoxins; an interferon such as interferon-alpha, -beta, and -gamma; colony stimulating factors (CSFs), e.g., M-CSF, GM-CSF, and G-CSF; interleukins (ILs), e.g., IL-1 to IL-10; superoxide dismutase; T-cell receptors; surface membrane proteins; decay accelerating factor; viral antigen such as, for example, a portion of the AIDS envelope; transport proteins; homing receptors; addressins; regulatory proteins; antibodies; and fragments of any of the above-listed polypeptides.

Several general embodiments are covered by the invention, including embodiments in which the therapeutically active substance in the dried pharmaceutical composition is hydrophilic and in which the dried pharmaceutical composition comprises an inert (not containing a drug) hydrophilic dried substance and a non-hydrophilic therapeutically active dried substance. It is known in the art that a combination of dried hGH with mannitol may be advantageous for dissolution of the

hGH powder. The term "micro-channel" as used in the context of the present patent application refers to a dried or lyophilized medication

As used herein, "pharmaceutical composition" or "medication" or "drug", used herein interchangeably, refers to a pharmaceutical composition comprising a therapeutically effective amount of an active substance wherein the composition may be dried or lyophilized while retaining a therapeutic activity.

In a preferred embodiment of the present invention, the solid drug composition can comprise more than one pharmaceutically active agent.

The pharmaceutical composition for use according to principle of the invention can be optimized to take into consideration issues like stability. In this specification the term "stable" refers to a composition that is robust enough to retain at least 80% of the active ingredient in its original chemical form for a period of over 12 months at ambient or below ambient temperatures.

The amount of therapeutically active substance in the pharmaceutical composition necessary to provide the desired amounts and concentration in the serum can be determined by known methods. Thus, the concentration and the quantity of the therapeutically active substance per dried pharmaceutically composition and per patch can be varied independently in order to achieve a desired effect.

Powder Patch

The present invention discloses for the first time the use of patches that comprise a dry pharmaceutical composition, as a delivery system for hydrophilic macromolecules, such as peptides or proteins, as well as for other highly water soluble drugs. After application of such a patch on the pretreated new skin environment, the pharmaceutical composition is dissolved in fluid that comes out of the microchannels, and is then absorbed through the micro-channels into the body. This approach is particularly suitable for drugs that do not irritate the skin even at high concentrations.

According to certain embodiments of the present invention, it is possible to monitor and to obtain a relative evaluation of the loss of fluids that come out from the microchannels in the new skin environment with respect to the loss of fluids that come out from the skin prior to ablation of the stratum corneum. This type of measurement is also termed herein "transepidermal water loss" or "TEWL", and is described in the foregoing examples.

Thus, a patch based on a drug in the solid state may have several advantages:

i. Improved stability, due to avoiding solvents and other excipients

ii. Relatively high delivery rates, due the delivery from a saturated solution or suspension.

iii. May enable production of thin and convenient patch, instead of reservoir patches, even for sensitive active materials that are not suitable for a drug-containing adhesive type of patch.

iv. Practical, as it enables usage of very small amounts of expensive substances.

Methods for preparing different types of powder patches, specifically methods that are suitable for accurately placing small amounts of an active drug, including proteins, as a dry substance onto a solid support from which they will be released are disclosed herein.

A. Printing

Printing methods encompass techniques in which small droplets of a solution or suspension of a pharmaceutical composition are placed on a uniform liner in a controlled manner. The droplets dry rapidly and leave solid dots of the pharmaceutical composition. The dose is accurately determined by the concentration of the solution or suspension and the configuration and programming of the manufacturing instrument. Besides the therapeutically active substance, the pharmaceutical composition may advantageously include other materials, such as solubility increasing agents.

In order to penetrate into the skin and the blood circulation, the pharmaceutical composition within the printed dots of the pharmaceutical composition on the liner, dissolves in the fluids that are exuded from the skin through microchannels.

Methods known in the art for applying droplets include a small volume (one to several microliter) syringe or an array of syringes, a combination of a small volume syringe or an array of syringes with a metering pump, an array of small pins, tips of the pins dipped in the solution/suspension, printing with a device like an ink jet printer, printing with a cartridge containing the solution of the pharmaceutical composition, spraying of a thin film of a solution of active drug on a liner and the like.

In one embodiment the printing pattern of the drug is similar to the pattern of the electrode array in the ViaDerm device. Thus the printed drug dots are placed over the microchannels in the new skin environment ensuring an immediate contact with all the microchannels. This approach reduces possible skin irritation as it avoids contact of

excess composition with the skin and enables usage of an adequate amount of the pharmaceutical composition required for efficient treatment.

To enable adhesion of the printed patch to the new environment skin the printing is prepared on a transdermal adhesive backing liner. Alternatively, a suitable adhesive can be printed between the prints of the drug, on a non-adherent liner.

B. Non-uniform liners

Suitable liners for this purpose are various liners with precise cavities. Basically the liner is dipped or soaked in the solution of the therapeutically active material, and then dried by air-drying or lyophilization or any other suitable means of drying or evaporation. The amount of solution of therapeutically active material that is applied on the liner is determined by the structure of the liner itself and its chemical and surface characteristics.

Various methods for preparing non-uniform dried drug-containing liners are known in the art including soaking a filter paper or a filter membrane with the solution of the drug and drying it, dipping a micronic net or screen into the active solution and drying it (as exemplified herein below), using a sheet with small and precise indentations or pores in a specific density or pattern and either filling the pores with the solution of the active drug, and drying or flipping the indentation so as to leave the active powder film on the protruding convexities, preparing a sheet with small projections on it then dipping the tips of the projections into the pharmaceutical active solution such that a small drop is left on each projection and drying.

Drying can be carried under controlled conditions for example by changing the temperature, humidity or pressure.

Various types of materials may be used to form the liners, including without limitation screens and fabrics in various pattern and synthetic woven meshes prepared from various polymers selected from the group of polyamide, polyester, polypropylene, Teflon, poly olefins such as polyethylene and polybutylene, polyurethane, polyvinyl butyrate, polysulphone, polyethersulphone, polyvinyl chloride, polycarbonate, polytetrafluoroethylene, polyvinylidene fluoride, cellulose acetate, cellulose triacetate, cellulose nitrate. A current preferred liner material is a polyester screen containing a mesh of 45 μm and 39% open area. Another preferred material is a dense nylon (polyamide) fabric (as exemplified herein below by Sefar Nitex™, G Bopp & Co Ltd, Derbyshire, UK).

C. Direct application of powder

A basic approach for the application of pharmaceutical powder is to directly apply the powder on the treatment site. According to one embodiment, spots of powder are embedded onto a soft flat sheet that is attached to the new skin environment by an additional adhesive layer. Alternatively, the sheet itself may be self-adherent. According to a second embodiment the powder is encapsulated within water-soluble films. The powder capsules can be prepared by distributing the powder over a water-soluble film containing an array of wells, filling the wells and removing excessive powder. The sheet is then covered with a similar sheet, such that the wells of both sheets are at similar positions. Alternatively, the pores in the water-soluble sheet are covered with a flat sheet which is a water-soluble film. The powder patch can be then attached to the skin such that either the flat sheet or the well-containing sheet is facing the new skin environment. The flat sheet may be also made of a non-soluble backing liner.

To enable adhesion to the new skin environment the drug powder can be dispersed over a liner which contains microscopic suction cups on its surface.

The powder patch according to the present invention, may be further incorporated into a medical patch. The medical patch comprising the powder patch may further comprise at least one of the following: a backing layer, an adhesive, preservatives, plasticizers, anti-oxidants, buffering agents, a suitable microporos liner layer such that the drug containing layer is disposed between the backing layer and the microporos liner layer, and other additives as are well known in the art.

The term "backing layer" is intended any protective layer not permeable to the drug that is provided to physically seal and hence protect the patch, specifically, the drug containing layer. The backing layer may be made of a polyester, polyethylene or polypropylene.

Application of a medical patch to the new skin environment is accomplished after at least partial removal of any covering or packaging, before use. This exposes the drug-containing layer, which may itself have adhesive properties, or may further comprise an adhesive layer attached to the drug-containing layer. Proper adherence to usage instructions generally ensures that the patch can be placed in a sterile manner.

Devices for enhancing transdermal delivery of dried or lyophilized medication

The system of the present invention further contains an apparatus for enhancing transdermal delivery of a substance. According to a principle of the invention the

apparatus is used to generate a new skin environment through which a dried or lyophilized medication is delivered efficiently.

In preferred embodiment of the present invention, the apparatus for enhancing transdermal delivery of a substance using RF energy is as disclosed in US Patent 6,148,232 and continuations thereto, comprising: an electrode cartridge, optionally removable, comprising at least one electrode and a main unit wherein the main unit loaded with the electrode cartridge is also denoted herein ViaDerm.

The control unit is adapted to apply electrical energy to the electrode typically by generating current flow or one or more sparks when the electrode cartridge is in vicinity of the skin. The electrical energy in each electrode within the electrode array causes ablation of stratum corneum in an area beneath the electrode, thereby generating at least one micro-channel.

The control unit comprises circuitry which enables to control the magnitude, frequency, and/or duration of the electrical energy delivered to an electrode, in order to control current flow or spark generation, and consequently to control the dimensions and shape of the resulting micro-channel. Typically, the electrode cartridge is discarded after one use, and as such is designed for easy attachment to the main unit and subsequent detachment from the unit.

To minimize the chance of contamination of the cartridge and its associated electrodes, attachment and detachment of the cartridge is performed without the user physically touching the cartridge. Preferably, cartridges are sealed in a sterile cartridge holder, which is opened immediately prior to use, whereupon the main unit is brought in contact with a top surface of the cartridge, so as to engage a mechanism that locks the cartridge to the main unit. A simple means of unlocking and ejecting the cartridge, which does not require the user to touch the cartridge, is also provided.

Optionally the electrode cartridge may further comprise means to mark the region of the skin where micro-channels have been created, such that a medical patch can be precisely placed over the treated region of the skin. It is noted that micro-channel generation (when practiced in accordance with the techniques described in the above-cited US patent or continuation patent applications to Avrahami et al., assigned to the assignee of the present patent application) does not generally leave any visible mark, because even the large number of micro-channels typically generated are not associated with appreciable irritation to the new skin environment.

Methods for using the system of the invention

The current invention also provides a method for treatment with a dried or lyophilized medication using the system of the invention. In general embodiments, the procedure for forming the new skin environment comprises the step of placing over the skin the apparatus for generating at least one micro-channel. Preferably, prior to generating the micro-channels the treatment sites will be swabbed with sterile alcohol pads. Preferably, the site should be allowed to dry before treatment.

In preferred embodiments of the current invention, the type of apparatus used to generate micro-channels is disclosed in US 6,148,232 and International Patent Application PCT/IL02/00319. The apparatus, containing the electrode array, is placed over the site of treatment, the array is energized by RF energy, and treatment is initiated. In principle, the ablation and generation of micro-channels is completed within seconds. The apparatus is removed after micro-channels are generated at limited depth, preferably limited to the depth of the SC and the epidermis. Any patch known in the art that is suitable for usage in the system of the invention as described above, comprising a therapeutically active agent, is attached to the new skin environment.

According to preferred embodiments of the current invention, for other applications the micro-channels may be generated separately or simultaneously with the application of a medical patch. Among the other applications, the system may include a medical patch comprising an adhesive cut-out template which is placed on the skin, and through which the cartridge is placed to treat the region of skin exposed through the template. The dried or lyophilized medication, contained within a printed patch or any other suitable patch according to embodiments of the present invention, is attached to the template which is to be placed over the treated region of skin. In these applications, after removing a protective backing, the template portion of the medical patch is placed on the skin and secured by the adhesive. An electrode cartridge is then affixed to the handle, the user holds the handle so as to place the cartridge against the region of skin inside the template, and the electrodes are energized to treat the skin. Subsequently, the cartridge is discarded. A protective covering is then removed from the medicated matrix by pulling on a tab projecting from the covering, so as to concurrently lift and place the medicated matrix over the treated region of skin. It is noted that the integration of the template and the patch into a single unit assists the user in accurately placing the

medicated pad onto the treated area of skin. Utilizing the system of the invention in this manner becomes advantageous for disinfected applications.

For still other applications, an integrated electrode/medicated pad cartridge is used, to provide a practical apparatus as disclosed in International Patent Application PCT/IL02/00376 which is assigned to the assignee of the present patent application and incorporated herein by reference and is also denoted MicroDerm. In these applications, the cartridge comprises an electrode array, a controlled unit and a medicated pad. Accordingly, no template is typically required. The user places the electrodes against the skin and this contact is sufficient to initiate current flow or spark formation within the electrode and the subsequent formation of micro-channels. An adhesive strip, coupled to the bottom of the medicated pad, comes in contact with and sticks to the skin when the electrodes are placed against the skin. A top cover on the medicated matrix is coupled to the electrode region of the cartridge, such that as the electrode region, fixed to the handle, is removed from the skin the top cover is pulled off the medicated pad and the pad is concurrently folded over the treated region of skin. This type of application eliminates the need for the user to touch any parts of the electrode cartridge or the medicated pad, thus substantially reducing or eliminating the likelihood of the user contaminating the apparatus.

In a preferred embodiment, current may be applied to the skin in order to ablate the stratum corneum by heating the cells. In one preferred embodiment, spark generation, cessation of spark generation, or a specific current level may be used as a form of feedback, which indicates that the desired depth has been reached and current application should be terminated. For these applications, the electrodes are preferably shaped and/or supported in a cartridge that is conducive to facilitating ablation of the stratum corneum and the epidermis to the desired depth, but not beyond that depth. Alternatively, the current may be configured so as to ablate the stratum corneum without the generation of sparks.

Generally preferred embodiments of the present invention typically incorporate methods and apparatus described in International Patent Application PCT/IL02/00376 entitled "Monopolar and bipolar current application for transdermal drug delivery and analyte extraction," which is assigned to the assignee of the present patent application and incorporated herein by reference. For example, this application describes maintaining the ablating electrodes either in contact with the skin, or up to a distance of about 500 microns therefrom. The application further describes spark-induced ablation

of the stratum corneum by applying a field having a frequency between about 10 kHz and 4000 kHz, preferably between about 10 kHz and 500 kHz.

Alternatively or additionally, preferred embodiments of the present invention incorporate methods and apparatus described in International Patent Application PCT/IL02/00319 entitled "Handheld apparatus and method for transdermal drug delivery and analyte extraction," which is incorporated herein by reference.

Still further alternatively or additionally, preferred embodiments of the present invention incorporate methods and apparatus described in the above-cited US Patent 6,148,232 to Avrahami, which is assigned to the assignee of the present patent application and incorporated herein by reference.

In some preferred embodiments of the present invention, the cartridge supports an array of electrodes, preferably closely-spaced electrodes, which act together to produce a high micro-channel density in an area of the skin under the cartridge. Typically, however, the overall area of micro-channels generated in the stratum corneum is small compared to the total area covered by the electrode array.

In further preferred embodiments of the present invention, a concentric electrode set is formed by employing the skin contact surface of the cartridge as a return path for the current passing from the electrode array to the skin. Preferably, the cartridge has a relatively large contact surface area with the skin, resulting in relatively low current densities in the skin near the cartridge, and thus no significant heating or substantial damage to the skin at the contact surface.

In proximity to each electrode in the electrode array, by contrast, the high-energy applied field typically induces very rapid heating and ablation of the stratum corneum.

Having now generally described the invention, the same will be more readily understood through reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

Human growth hormone (hGH) is a 22 kDa polypeptide hormone that was chosen, in its recombinant form (rhGH) to represent the transdermal delivery capacity of a large, hydrophilic molecules using a powder patch and ViaDerm technology.

GH is produced by the pituitary gland (hypophysis) and acts in several ways and on several targets. A distinctive role attributed to GH, and which is of our interest in this

study, is acting on liver cells (hepatocytes) to produce IGF-I, one of many growth promoters produced by the body. As GH is the main trigger for the production of IGF I it presents us with the possibility of analyzing not only the uptake of GH but also its activity by measuring IGF-I levels.

In hypophysectomized animals, IGF I levels are expected to be negligible without treatment and dose dependant in treated animals.

The test article chosen for this study is GENOTROPIN® (Pharmacia & Upjohn, Sweden) which contains a recombinant hGH (one dose contains 16IU, 5.3 mg) synthesized by a modified strain of E. Coli and designed for subcutaneous injection and mannitol (1.5 mg). The other components in a reconstituted single dose of GENOTROPIN® are: glycine (2 mg), mannitol (39.5 mg), sodium dihydrogen phosphate anhydrous (0.29 mg), disodium phosphate anhydrous (0.28 mg), m-cresol (3 mg) and water (1 ml).

The presence of mannitol, which is a hygroscopic substance, in the rhGH composition of GENOTROPIN®, is important. According to the principle of the present invention the powder patches are applied on a pre-treated skin containing microchannels such as those formed by ViaDerm. The pharmaceutical powder which is hygroscopic due to its mannitol content, dissolves in the exudates from the microchannels hence enabling an efficient transdermal delivery of the drug.

EXAMPLE 1. Preparation of rhGH printed powder patch

Essentially, the printed-patches were prepared by spotting precise small droplets of rhGH solution on top of a commercial suitable backing liner in a predetermined pattern, also termed hereinafter "printing", following by drying at room temperature.

Printing of rhGH solution was carried out with a microliter syringe, fitted with blunt needle. The printing was performed using a digital controlled XYZ dosing machine, controlled by Basic program for the predetermined pattern of 144 microliter sized droplets, in a 12 x 12 array. Total printing area was 1.44 cm^2.

a. Preparation of rhGH solutions

rhGH solutions at various concentrations, from 8.8 mg/ml to17.6 mg/ml, were prepared by dissolving GENOTROPIN® in deionized water. Each solution was transferred to a 100 µl syringe and air bubbles from the syringe were removed.

b. Printing the rhGH solutions

For the preparation of a patch with the required amount of rhGH the volume of each droplet was calculate according to the concentration of the rhGH in the solution and accordingly the syringe's plunger displacement which is required per one droplet printing was adjusted, wherein the range of 0.035 - 0.105mm corresponded to 0.09 - 0.18 μl. This range of displacement was fed into a Basic program that controls the printing. Next, the Backing layer film (DOW BLF2080™, The Dow Chemical Company, MI, USA) was placed flat with the bright side up on a flat metal block. The syringe containing the rhGH solution was loaded into the XYZ dosing machine which then placed measured rhGH drops on the backing liner. It should be noted that within a few minutes the drops started to dry consecutively. Once the 144 dots array of printed droplets was formed the printing of new array started on a new position. According to this procedure it was possible to form up to 6 arrays on a 5.5 x 1.6" backing liner. Sections, 2x2 cm^2, of the printed 144 dotted arrays (e.g. Fig. 1) were kept at 4°C in close vials.

EXAMPLE 2. Preparation of rhGH powder-patches using non-uniform liners

The aim of the experiment is to create patches in which the pharmaceutically active powder is uniformly dispersed over a liner. In this experiment a polyester screen was used as a liner. Powder rhGH patches were prepared by applying 10 μl of rhGH solution (18.5 μg/ μl) over pieces (15x15mm^2, 7.7mg) of polyester screen (mesh of 45 μm and 39% open area) following drying by air. This procedure was repeated 5 times for each preparation. Figure 1 represents a screen containing 0.5 mg of rhGH which was dispersed over the screen. The figure indicates that in this preparation most of the rhGH powder was located at the rim of the grid rather than being uniformly distributed.

To test the deposition of large amounts of hydrophilic substance on this type of polyester screens a diluted rhGH solution was used. A few drops of the diluted rhGH solution were applied on pieces of the polyester screen following air-drying. The powder that was attached to the screen after this procedure was not uniformly distributed as shown in Fig. 2. In order to emphasize the image of the powder-pattern that is left on the screen after this procedure, a mixture of mannitol and Methylene Blue was applied over a polyester screen (dark lines in Fig. 3).

In order to examine whether increased powder load contributes to uniform distribution of the powder that is left after the water evaporates dry patches were prepared with sucrose instead of a drug. Square pieces of polyethylene screen (15x15mm^2, 7.8mg, mesh of 45 μm and 39% open area) were immersed in a solution of 50% sucrose (commercial grade) following agitation of the screen to remove air entrapped within the screen pieces. Screen pieces were dried to remove excess sucrose solution. Dry sucrose was shown to fill evenly the square holes in the screen (Fig. 4).

The total weight of the sucrose-loaded screen was 10.3 mg corresponding to 2.5mg sucrose which is 32% of the screen's initial weight. Figure 5 represent images of a polyester screen before (left panel) and after (right panel) immersing in sucrose solution and drying. The uniform distribution of the dried sucrose is clearly observed in this figure (right panel).

EXAMPLE 3. Transdermal permeation of powder rhGH in hypophysectomized rats – blood levels and protein activity

Materials and Methods

Animals: Rats, males, 250g, Sprague Dawley, hypophysectomized at Harlan USA labs. In order to minimize the damage caused by the hypophysectomy the animals were treated with thyroxine sodium salt (ELTROXIN™, Glaxo GmbH, Bad Oldesole, Germany) and HYDROCORTISONE from arrival until the start of the trial.

Test article: The dried fraction of GENOTROPIN® (rhGH and mannitol) was used for the transdermal applications. This fraction was spread on a hypoallergenic clear medical tape (Kendall Curity®, Emergency Medical Products Inc., USA) in doses specified below, and placed directly onto the skin as a transdermal patch. For the subcutaneous treatments, reconstituted GENOTROPIN® was used.

Experimental setup: 24 rats, given food and drink (0.45% NaCl in water) ad libitum, were divided into 4 groups of 6:

Group 1: ~0.8mg/rat rhGH transdermal patch on ViaDerm treated skin (Table 1).

Group 2: ~0.8mg/rat rhGH transdermal patch on intact skin.

Group 3: Subcutaneous (SC) injection of rhGH, 150μg/rat (0.33ml/rat).

Group 4: Untreated.

The transdermal groups (1 and 2) received a treatment including: Shaving, drying, baseline TransEpidermal Water Loss measurement (TEWL; DERMALAB® Cortex Technology, Hadsund, Denmark), two ViaDerm applications of 200 micropores/cm^2

(placebo for Group 2), second TEWL measurement and patch application. At the end of the study all animals were sacrificed by an IV overdose of sodium-pentobarbital (140mg/kg).

ViaDerm parameters: burst length – 500μsec, starting amplitude – 250 V, number of bursts – 5 and applications per site - 2 (200 micropores/cm^2).

Blood samples were collected from the tail at times: 0,2,4,6,12,24 hours.

Blood sampling: Blood samples (0.5 ml/rat) were withdrawn at 6 time points, t=0, 2,4,6,12 and 24 hours, from the tail end of anesthetized rats (20mg/rat ketamine, intramuscular).

Serum analysis: rhGH in the serum was detected using an Elisa kit (DSL-10-1900; Diagnostic Systems Laboratories, TX, USA) specific for rhGH. The kit does not detect endogenous rat GH. IGF-I was detected according to RIA protocol (Endocrine, Vol. 16, no. 1, 1-6, October 2001). Utilizing this detection protocol it is impossible to distinguish between IGF I synthesis which is regulated by endogenous GH to IGF I synthesis that is regulated by exogenous GH.

Results

1. rhGH in the serum

The average concentrations of rhGH in the serum are plotted in Fig. 6. Group 1 (ViaDerm + rhGH) demonstrated an average profile with a peak at 4 hours post administration. This peak was lower and was achieved later than the maximal concentration of rhGH in the SC group (Group 3). Groups 2 (rhGH on untreated/intact skin) and 4 (no treatment) demonstrated negligible concentrations of rhGH in the serum as expected. In Group 3 (subcutaneous injection) 5 out of 6 rats demonstrated a typical injection profile with peak concentration 2 hours post injection and after 4 hours in the sixth rat. Although rhGH decayed in the serum of all rats in a similar pattern, the average values exhibited a large variance, larger than the variance observed in the ViaDerm treated group.

2. Pharmacokinetics - AUC (area under the curve) calculations for rhGH

ViaDerm treated group (Group 1) - 3052μg/hr/ml absolute AUC value and 381.6 μg/hr/ml normalized AUC for 0.1g rhGH.

SC group (Group 3) - 1692μg/hr/ml absolute AUC value and 1128 μg/hr/ml normalized AUC for 0.1g rhGH.

According to these calculations the ViaDerm treated group demonstrated a bioavailability value of 33.8% compared to the SC group. AUC values were improved with the use of lower doses of rhGH and increased uniformity of spread within the patches using printed patches as shown in the following example.

3. IGF I in the serum

The average concentrations of IGF-I in the serum are plotted in Fig. 7. Group 1 (ViaDerm + rhGH treated) demonstrated elevation of IGF I indicating that the activity of rhGH is maintained using ViaDerm + rhGH powder patch system. The maximal average concentration was observed at 12 hours post treatment and between 6-12 hours post treatment for the individual rats. Group 2 (rhGH only) demonstrated low level of IGF I throughout the treatment period. This result was coherent with the low rhGH levels in the serum of this group (see Fig. 6). Group 3 (subcutaneous injection) demonstrated the anticipated elevation of IGF I with peak concentration at 12 hours post treatment for all rats on average and for each rat individually. These results were similar to IGF I levels in the ViaDerm +rhGH group (Fig. 7). Group 4 (no treatment) demonstrated an expected low level of IGF I throughout the treatment period verifying the results obtained for rhGH.

The similar activity in both the ViaDerm+rhGH group and SC groups could be further rationalized by the fact that the dose used in this study for the former group was very high (~0.8 mg/patch), higher than the absorption capability of the rat. This may also lead to the AUC results achieved.

The foregoing example provides a patches and methods for improving the accuracy of dosage per patch and the uniformity of spread on each patch.

EXAMPLE 4. Bioavailability of rhGH in hypophysectomized rats using printed patches

Materials and Methods

The materials and methods applied in this example were similar to those in example 3 except from the following points:

a) The animals were treated with ELTROXIN™ and hydrocortisone only until 10 days before initiating the treatments.

b) The test article was a printed patch of rhGH in two doses: 0.15mg/patch and 0.5mg/patch. The patches were composed of a backing liner (DOW BLF2080™, The Dow Chemical Company, MI, USA) on which drops of GENOTROPIN® were evenly

placed. All the patches contained 144 drops over an area 1.4X1.4 cm^2. The printed patch was attached to the skin by a fixing patch, 2cm X 2cm with 300μm thick (wet) glue (DURO-TAK™ 3872516; National Starch & Chemical Pty Ltd, NSW, Australia) on the backing liner.

c) The experimental setup included 2 groups of 3 rats each:

Group 1: Treated with ViaDerm + one 0.15 mg printed patch.

Group 2: Treated with ViaDerm + one 0.5 mg printed patch.

Results

1. Printed patches

Printed patches were produced in two doses, 0.15mg and 0.5mg of rhGH. An overview of a representative printed patch (Fig. 8A) and of individual printed dots within the patch (Fig. 8B) reveals a relatively uniform distribution of the dots.

Patches from the same production batch were analyzed by HPLC to measure the actual quantity of rhGH per patch with respect to the anticipated quantity (Fig. 9). rhGH concentration in the 0.15mg printed patches was found 2-9% higher than expected and in the 0.5mg printed patches 10-19% higher than expected.

2. rhGH in the serum

TEWL results were all within the set limits, namely, pretreatment TEWL levels were lower than 8.5 $g/h/m^2$ and TEWL differences before and after ViaDerm treatment were higher than 10 $g/h/m^2$.

Group 1 (ViaDerm + 0.15mg printed patch) demonstrated an average profile with a peak at 4 hours post administration (Fig. 10). Group 2 (ViaDerm treated + 0.5mg printed patch) demonstrated an average profile with a peak at 6 hours post administration. In both groups the results for 4 and 6 hours were high and similar. In Group 1 there was a considerable drop between 6 and 12 hours, while in Group 2 the high levels were maintained until 12 hours and the drop occurred between 12 and 24 hours post application. The two doses of printed patches demonstrated a significant difference in rhGH serum level per time point, indicating that these doses provided a satisfying experimental setup for verifying dose dependencies.

A comparison was carried out between sera levels of rhGH after application of rhGH printed patches and sera levels of rhGH after subcutaneous injection of rhGH (see Example 3), following ViaDerm treatment (Fig. 10). The peak achieved by subcutaneous injection appeared earlier than in the two groups of printed patches (2

hours). The peak concentration of subcutaneous injection was higher than the 0.15 mg printed patch group and lower than the 0.5 mg printed patch group.

3. Pharmacokinetics:

Representative AUC values normalized to administration of 0.1mg rhGH, wherein 100% refers to SC injection, are shown in Fig. 11. AUC values for each group treated with rhGH in the previous example and the current one, were as follows:

a) Group 1 (ViaDerm + 0.15mg printed patch) 1594μg-hr/ml absolute value, 1063μg-hr/ml normalized to 0.1mg rhGH.

b) Group 2 (ViaDerm + 0.5mg printed patch) 6563μg-hr/ml absolute value, 1313μg-hr/ml normalized to 0.1mg rhGH

c) Group 3 of Example 3 (SC injections of 0.15mg /rat) - 1692μg-hr/ml absolute value, 1128μg-hr/ml normalized for 0.1mg rhGH.

According to these calculations Group 1 of the printed patches demonstrated a bioavailability value of 95.2% compared to the SC injections group and Group 2 of the printed patches demonstrated a bioavailability value of 118% compared to the SC injections group.

EXAMPLE 5. ViaDerm device: Specifications and Performance in vivo

The ViaDerm apparatus that was used to generate micro-channels in the pre-clinical and clinical studies described herein, is disclosed in US Patent 6,148,232 and International Patent Applications PCT/IL02/00319 and PCT/IL02/00376. In brief, ViaDerm is comprised of the following:

1. A reusable main unit comprising a control unit which generates an RF electrical current (Fig. 12).

2. A disposable electrode cartridge (Fig. 13) comprising an array of microelectrodes attached onto the end of the main unit.

Histological studies of micro-channels formed by ViaDerm within a porcine skin showed that the dimensions of the micro-channels are controllable and precise: each micro-channel was 30 μm in width and 50-100 μm in depth. In the porcine skin, wherein the epidermis depth is about 40 μm, these micro-channels penetrated into the dermis. However in humans, in whom epidermis depth is about 100 μm, such micro-channels reside within the limits of the epidermis. In addition, it should be noted that the micro-channels were very localized, and the skin surrounding the micro-channels

maintained its normal structure (Fig. 14).

TEWL was measured in skin sections of porcine ear after generating different quantities of micro-channels (Fig. 15). TEWL linearly increased with increasing the number of micro-channels.

EXAMPLE 6. Clinical studies of ViaDerm performance

Materials and Methods

Study subjects. ViaDerm performance was assessed by a study conducted with twenty healthy, adult volunteers, 10 males and 10 females. The study was conducted at ClinRx a Clinical research organization under Good Laboratory Practice (GLP) standards. Each subject received 10 treatments, in a randomized manner such that a given treatment was applied to different subjects and/or in each subject at different sites.

Treatment protocol. The treatment sites were the inner arm and hand. Each treatment included the following steps: preparing the skin (cleaning); measuring TEWL (T_{0-}) at a treatment site and an adjacent site; placing ViaDerm upon the treatment site and activating the electrodes with controlled RF electrical energy; measuring TEWL immediately at the treatment site and the adjacent site; Scoring for erythema, edema and tolerability (T_{0+}), at the treatment site; covering the treatment site with a sterile hydrogel (VIGILON™, The Medical Supply Company Inc., NY, USA) patch; Removing the patch at T=24 hr; measuring TEWL at the treatment site and the adjacent site; Scoring for erythema and edema at the treatment site at T=25hr and 48hr.

ViaDerm performance. Measuring Transdermal Water Loss (TEWL) at a skin site treated with ViaDerm in comparison to an adjacent untreated skin assessed formation of micro-channels. Safety of ViaDerm was evaluated by measuring irritation (erythema and edema) at the treatment site using a scale of zero to eight in accordance with Draize irritation index (Table 4). The response to irritation induced by ViaDerm was assessed by a Cumulative Irritation Index (Table 5). Skin tolerability was studied by measuring pain on a 100mm Visual Analog Scale (VAS) following ViaDerm treatment.

Results

a. Safety evaluation.

Erythema was observed at sites treated with ViaDerm and covered with a patch for 24 hr. This erythema disappeared 24 hr after removal of the patch. Erythema was not observed in non-treated adjacent sites. The maximal mean value of erythema was 0.81

accounting for a very slight erythema according to table 5. The different application sites exhibited similar irritation scores.

Edema was observed at sites treated with ViaDerm and covered with a patch for 24 hr. This edema disappeared 24 hr after removal of the patch. Edema was not observed in non-treated adjacent sites. The maximal mean value of edema was 0.25 accounting for negligible edema according to Table 5. The different application sites exhibited similar irritation scores.

The maximal mean combined irritation index (erythema and edema) was 0.75 for the ViaDerm treatment sites when occluded and 0.5 for the adjacent non-occluded sites accounting for a minor response.

TABLE 4. Draize irritation index.

Erythema and Eschar Formation	**Grade**
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4
Edema formation	**Grade**
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Total possible score for irritation	**8**

TABLE 5. Cumulative Irritation Index.

Response category	**Mean Score**
Negligible	0 to 0.4
Slight	0.5 to 1.9
Moderate	2.0 to 4.9
Severe	5.0 to 8.0

b. Tolerability evaluation

Pain scores were in the range of 0-50mm. The pain score per subject was an average from 10 ViaDerm applications. The average values (per site of treatment) ranged from 2.1mm to 7.02mm. Those values are considered negligible.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without undue experimentation and without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. The means, materials, and steps for carrying out various disclosed functions may take a variety of alternative forms without departing from the invention. Thus the expressions "means to..." and "means for...", or any method step language, as may be found in the specification above and/or in the claims below, followed by a functional statement, are intended to define and cover whatever structural, physical, chemical or electrical element or structure, or whatever method step, which may now or in the future exist which carries out the recited function, whether or not precisely equivalent to the embodiment or embodiments disclosed in the specification above, i.e., other means or steps for carrying out the same functions can be used; and it is intended that such expressions be given their broadest interpretation.

CLAIMS

1. A system for transdermal delivery of a dried pharmaceutical composition, comprising: an apparatus for facilitating transdermal delivery of a drug through skin of a subject, said apparatus capable of generating at least one micro-channel in an area on the skin of the subject, and a patch comprising a therapeutically effective amount of the dried pharmaceutical composition.

2. The system according to claim 1 wherein the dried pharmaceutical composition is hydrophilic.

3. The system according to claim 2 wherein the dried pharmaceutical composition comprising at least a therapeutically active agent.

4. The system according to claim 3 wherein the therapeutically active agent is selected from the group of polypeptides, peptides, polynucleotides, oligonucleotides, steroid hormones, growth factors and hormones.

5. The system according to claim 3 wherein the therapeutically active agent is a human growth hormone.

6. The system according to claim 3 wherein the dried pharmaceutical composition further comprises at least one hydrophilic agent.

7. The system according to claim 6 wherein the hydrophilic agent is mannitol.

8. The system according to any of claims 1 through 7 wherein the patch further comprising at least one component selected from: a backing layer, an adhesive, an anti-oxidant, a buffering agent, a preservative.

9. A printed patch consisting essentially of a dried pharmaceutical composition.

10. The printed patch according to claim 9 wherein the dried pharmaceutical composition is hydrophilic.

11. The printed patch according to claim 10 wherein the dried pharmaceutical composition comprises at least one therapeutically active agent.

12. The printed patch according to claim 11 wherein the therapeutically active agent is selected from the group of polypeptides, peptides, polynucleotides, oligonucleotides, steroid hormones, growth factors and hormones.

13. The printed patch according to claim 11 wherein the therapeutically active agent is human growth hormone.

14. The printed patch according to claim 11 wherein the dried pharmaceutical composition further comprises at least one hydrophilic dried agent.

15. The printed patch according to claim 14 wherein the hydrophilic agent is mannitol.

16. The patch according to any of claims 9 through 15 further comprising at least one component selected from a backing layer, an adhesive, an anti-oxidant, buffering agents, a preservative.

17. The system according to claim 1 wherein the patch is according to any one of claims 9 through 16.

18. The system according to claim 1 comprising an apparatus for facilitating transdermal delivery of a drug through skin of a subject, said apparatus comprising:

a. an electrode cartridge comprising at least one electrode; and
b. a main unit comprising a control unit which is adapted to apply electrical energy to the electrode when the electrode is in vicinity of the skin, typically generating current flow or one or more sparks, enabling to cause ablation of stratum corneum in an area beneath the electrode, thereby generating at least one micro-channel.

19. The system according to claim 18 wherein the electrode cartridge is removable.

20. The system according to claim 18, wherein the electrode cartridge comprises a plurality of electrodes capable of generating a plurality of micro-channels of uniform shape and dimensions.

21. The system according to claim 18, wherein the electrical energy is of radio frequency.

22. A method for transdermal administration of a dried pharmaceutical composition containing a therapeutically active agent comprising:

(a) generating at least one micro-channel in a region of the skin of a subject, and

(b) affixing a patch comprising the dried pharmaceutical composition to the region of skin in which the micro-channels are present.

23. A method for transdermal administration of a dried pharmaceutical composition containing a therapeutically active agent comprising:

(a) generating at least one micro-channel in a region of the skin of a subject, and

(b) affixing a patch comprising the dried pharmaceutical composition to the region of skin in which the micro-channels are present, and

(c) attaining a serum concentration of the therapeutically active agent of at least 50 ng/ml.

24. The method according to any one of claims 21 to 23 wherein the dried pharmaceutical composition is hydrophilic.

25. The method according to claim 24 wherein the dried pharmaceutical composition comprising at least a therapeutically active agent.

26. The method according to claim 25 wherein the therapeutically active agent is selected from the group of polypeptides, peptides, polynucleotides, oligonucleotides, steroid hormones, growth factors and hormones.

27. The method according to claim 25 wherein the therapeutically active agent is a human growth hormone.

28. The method according to any one of claims 21 to 27 wherein the patch is a printed patch according to claim 9.

29. A method for preparing a printed patch containing a therapeutically active agent comprising:

a. preparing a pharmaceutical solution or suspension comprising at least one therapeutically active agent; and

b. placing at least one droplet of an accurate volume of the solution or suspension of (a) on a suitable matrix; and

c. drying the matrix of (b) wherein upon drying the therapeutic activity of the therapeutically active agent of (a) is retained.

For the applicants

Cynthia Webb

Webb & associates

Patent attorneys

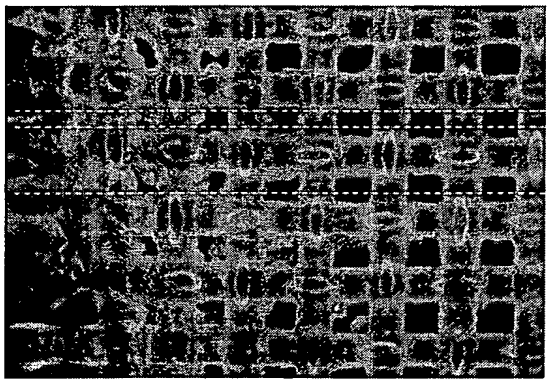

Figure 1

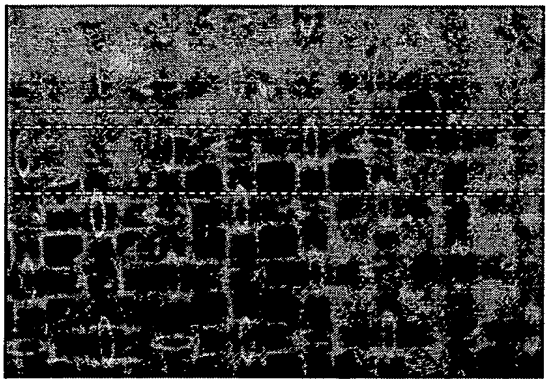

Figure 2

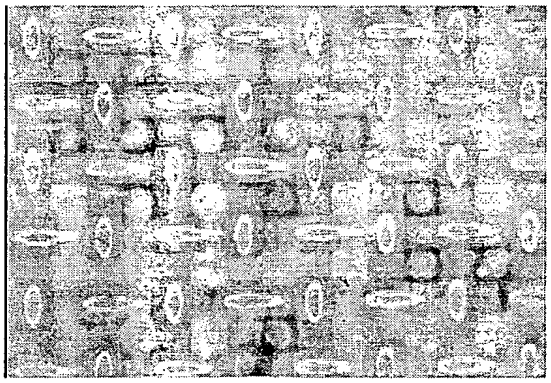

Figure 3

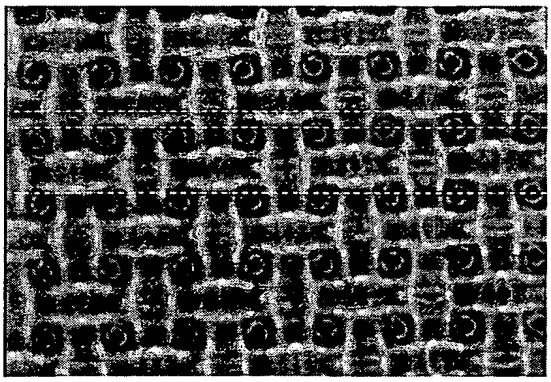

Figure 4

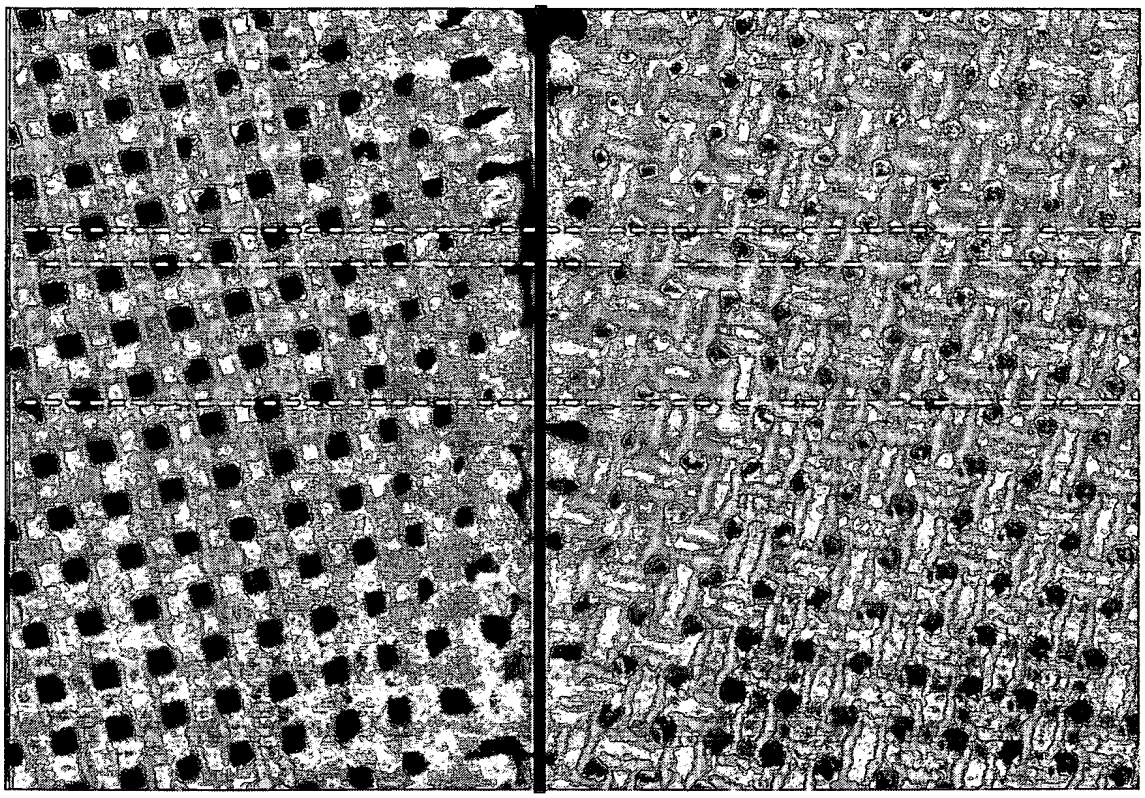

Figure 5

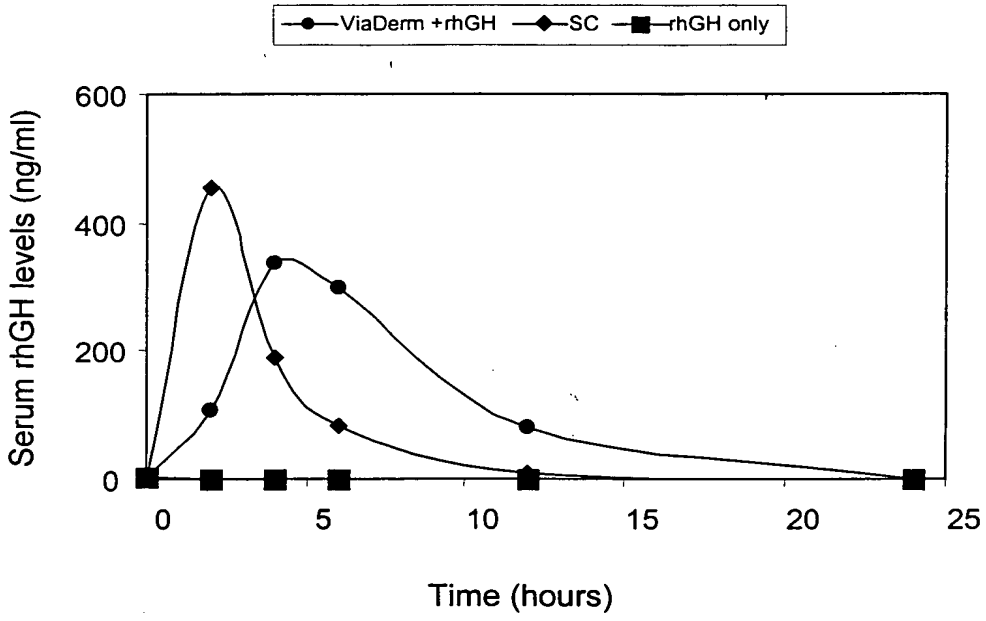
ViaDerm +rhGH
SC
rhGH only
Serum rhGH levels (ng/ml)
600
400
200
0
0
5
10
15
20
25
Time (hours)

Figure 6

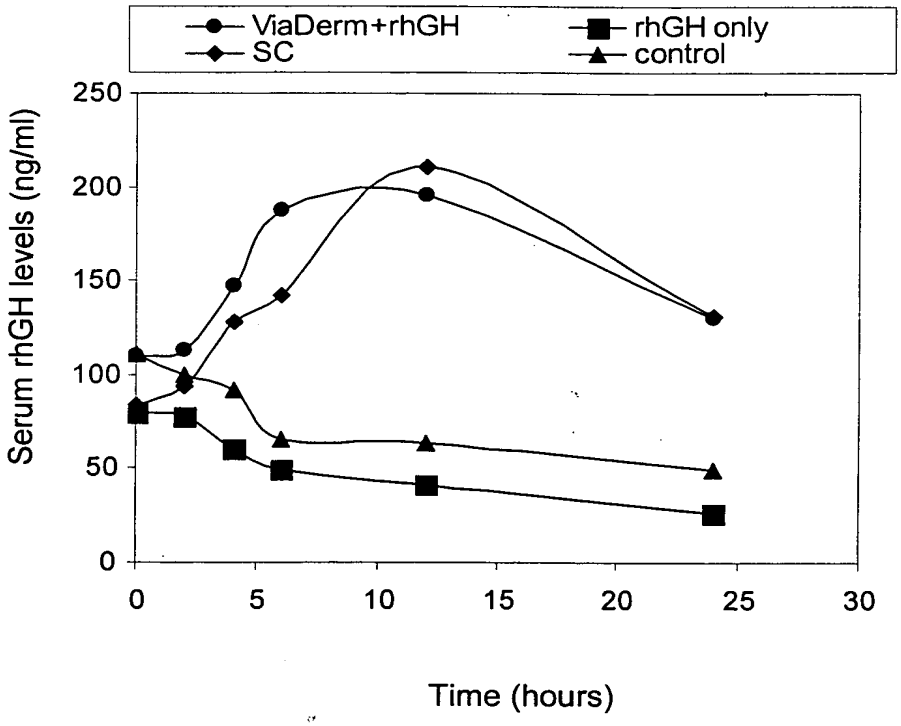
ViaDerm+rhGH
rhGH only
SC
control
Serum rhGH levels (ng/ml)
250
200
150
100
50
0
0
5
10
15
20
25
30
Time (hours)

Figure 7

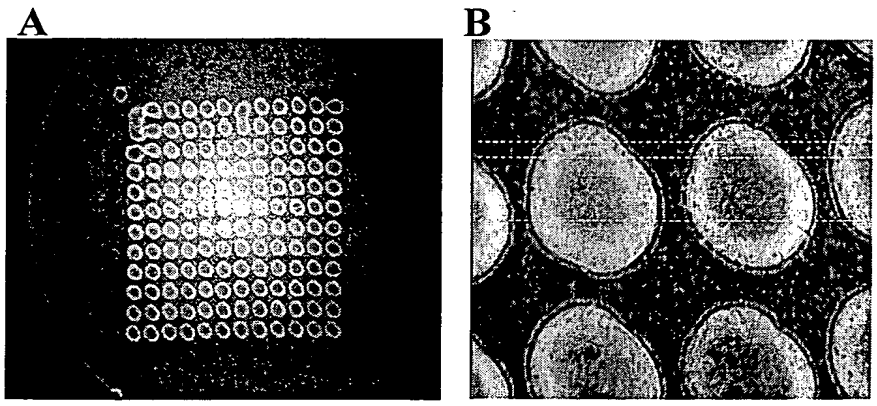

Figure 8

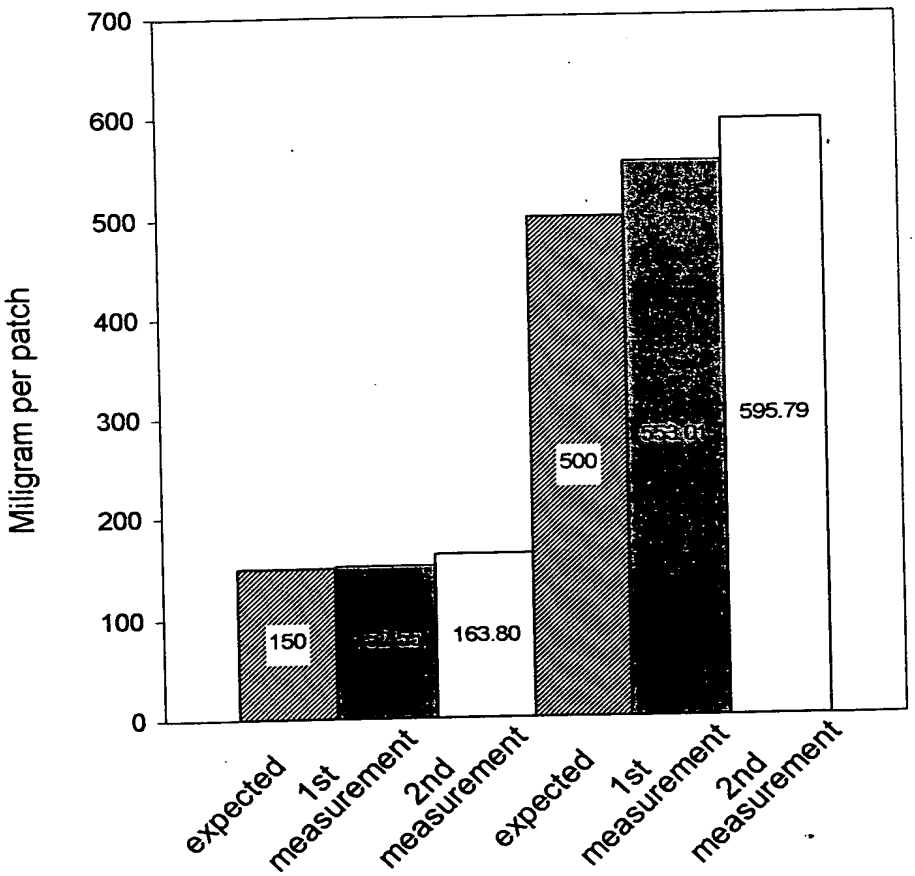
700
600
500
400
300
200
100
0
Miligram per patch
150
163.80
500
595.79
expected
1st measurement
2nd measurement
expected
1st measurement
2nd measurement

Figure 9

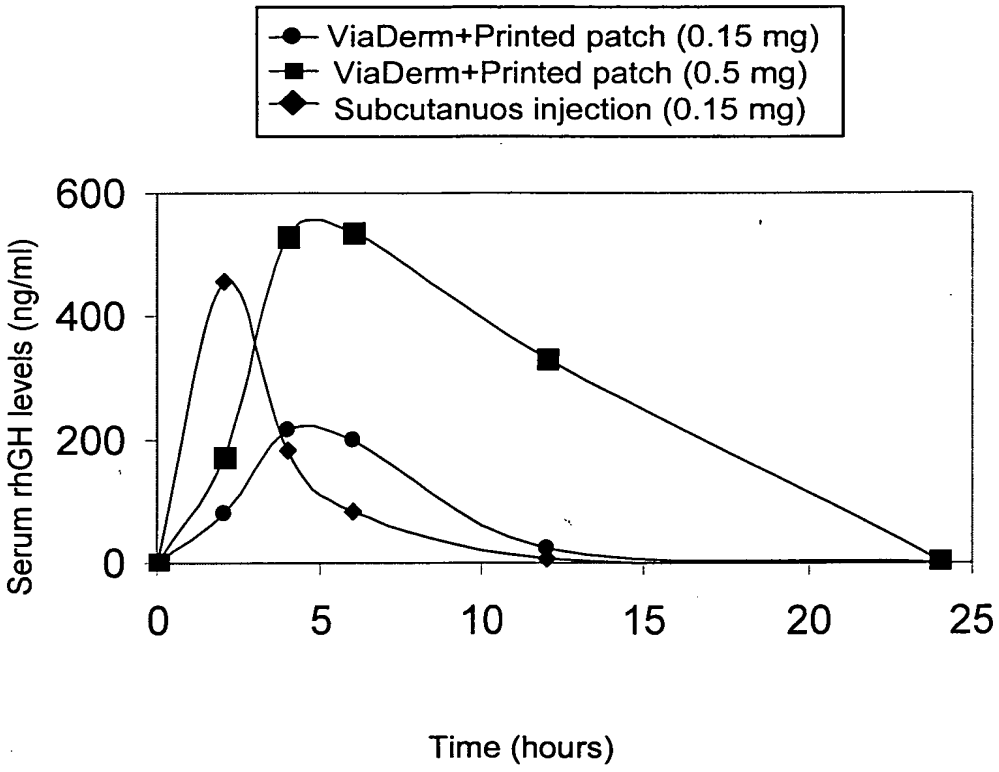
ViaDerm+Printed patch (0.15 mg)
ViaDerm+Printed patch (0.5 mg)
Subcutanuos injection (0.15 mg)
Serum rhGH levels (ng/ml)
600
400
200
0
0
5
10
15
20
25
Time (hours)

Figure 10

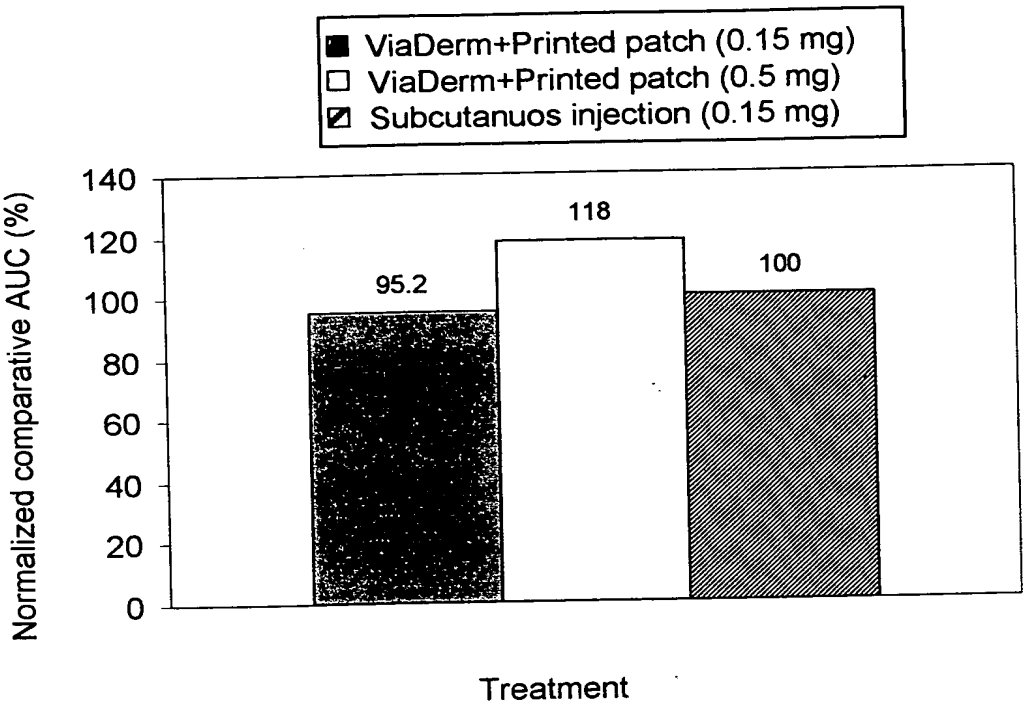
ViaDerm+Printed patch (0.15 mg)
ViaDerm+Printed patch (0.5 mg)
Subcutanuos injection (0.15 mg)
Normalized comparative AUC (%)
140
120
100
80
60
40
20
0
95.2
118
100
Treatment

Figure 11

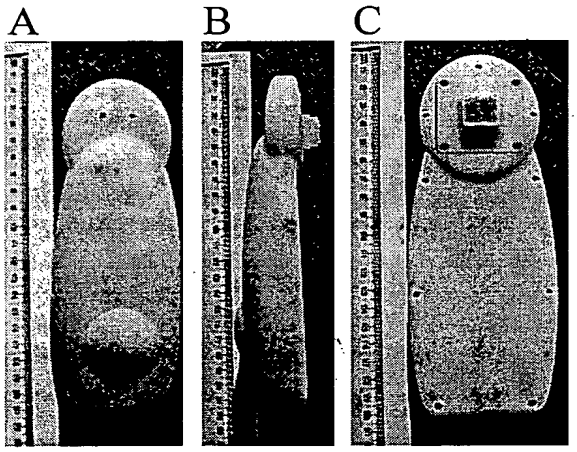

Figure 12

Figure 13

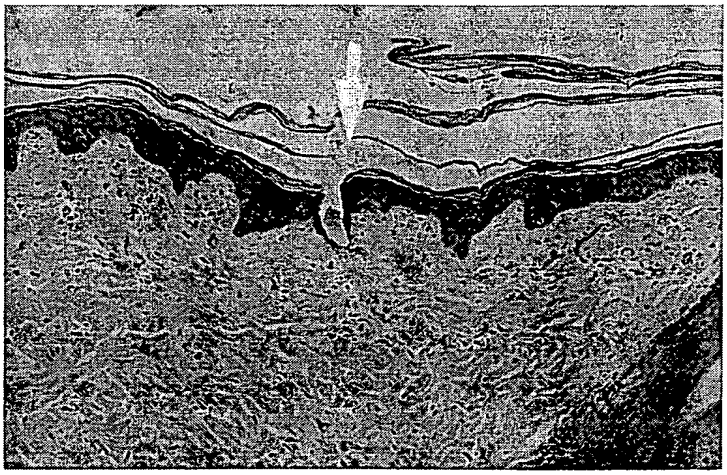

Figure 14

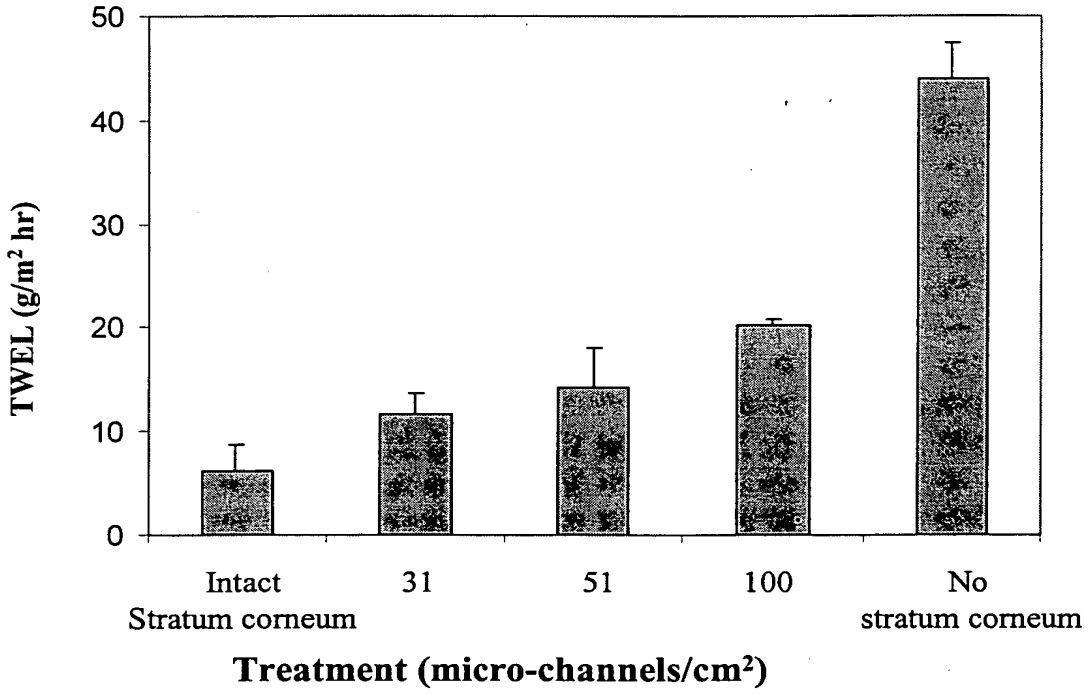
50
40
30
20
10
0
TWEL (g/m² hr)
Intact
Stratum corneum
31
51
100
No
stratum corneum
Treatment (micro-channels/cm²)

Figure 15